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09/755,701	01/05/2001	Allan S. Hoffman	UWOTL119001	3998

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/755,701	HOFFMAN ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,8,9,13-17,19,34-36 and 38-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,8,9,13-17,19,34-36, 38, 40, 41, 43-47* is/are rejected.

7)☒ Claim(s) *39 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered. Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 were pending. Applicants amended claims 4, 8, 36, 38, 39, 41, and 42. No claims were added or canceled. Therefore, claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are pending and examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The rejection denoted "A-C" under 35 U.S.C. § 112, second paragraph over the word phrase "vinyl type" is withdrawn in view of Applicants' amendments to the claims removing this term. The Davaran et al. rejections under 35 U.S.C. §§ 102 and 103 are also withdrawn in favor of the newly modified rejections set forth below.

New Rejections

Claims Rejections - 35 U.S.C. 102/103

3. Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 are rejected under 35 U.S.C. 102(b)

as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Davaran et al. (Davaran et al., "Hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydroyzable thioester bond" *Eur. Polym. J.* **1998**, *34(2)*, 187-192) as evidenced by Applicants' specification and Baroni et al. (Baroni et al., "Effect of ibuprofen and warfarin on the allosteric properties of haem-human serum albumin" *Eur. J. Biochem.* **2001**, 268, 6214-6220) and Ito et al. (Ito et al., "Control of Water Permeation by pH and Ionic Strength through a Porous Membrane Having Poly(carboxylic acid) Surface-Grafted" Macromolecules **1992**, 25, 7313-7316) and Theodore et al. (U.S. Patent No. 6,358,490) (Date of Patent is **March 19, 2002**).

For ***claim 3***, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is a organic molecule (e.g., see abstract wherein ibuprofen is disclosed).

For ***claim 4***, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component is a synthetic vinyl-type hydrophobic polymer, naturally derived polymer, a membrane disruptive peptide, or a phospholipid bilayer disrupting agent (e.g., see page 189, scheme 2 disclosing methacrylate "vinyl-type" polymer).

For ***claims 8 and 40***, Davaran et al. teach the composition of claims 36 or 38, wherein the pH-sensitive linkage is an ester (e.g. see Davaran et al., page 190, column 2, paragraph 2 wherein PEG is connected to the methacrylate via an ester linkage).

For ***claim 9***, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is coupled to either the hydrophilic or the hydrophobic component by a degradable or disruptable linkage (e.g., see abstract wherein ibuprofen is connected via a hydrolysable thioester linkage; see also figures 1-3 showing

hydrolysis rates).

For ***claim 13***, Davaran et al. teach the composition of claim 36, wherein the conjugate further comprises a ligand, wherein the ligand specifically binds to a target molecule (e.g., see abstract wherein ibuprofen is disclosed). Davaran et al. do not explicitly state that ibuprofen is a ligand for a target but the Examiner contends that this is an inherent property of ibuprofen as exemplified by Baroni (e.g., see Baroni et al., page 6215, column 2, first full paragraph, "Ibuprofen binds to Sudlow's site II [on HSA] with $K_d = 3.7 \times 10^{-7}$ M").

For ***claim 14***, Davaran et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is complexed to a component of the conjugate (e.g., see scheme 2 and experimental).

For ***claim 15***, Davaran et al. do not explicitly teach the composition of claim 36, wherein the pH sensitive linkage is hydrolyzed within about 30 to 60 minutes at a pH between 5.0 and 5.5. However, Davaran et al. discloses Applicants' preferred ester linkage and, as a result, the Examiner contends that this would be an inherent property of the conjugate (e.g., see arguments for claim 36 below).

For ***claim 34***, Davaran et al. teach the composition of claim 36 further comprising an agent, wherein the agent is a therapeutic, diagnostic, or prophylactic agent (e.g., see page 189, column 2, wherein a therapeutic drug is disclosed; see also abstract wherein ibuprofen is disclosed).

For ***claim 35***, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises a synthetic polymer (e.g., see Davaran et al., page

189, scheme 2).

For ***claim 36***, Davaran et al. teach hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydrolysable thioester bonds (e.g., see Davaran et al., title and abstract), which anticipates the claimed invention. For example, Davaran et al. teach a water-soluble hydrophilic conjugate having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage (e.g., see Davaran et al., page 189, scheme 2 showing conjugate with methacrylate hydrophobic component; see also page 190, column 2, paragraph 2 wherein the water-soluble PEG is linked via a pH sensitive ester bond to the methacrylate). Please note that Davaran et al. do no explicitly state that the ester bond in the PEGM is a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 but the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al. (e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5). When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently

possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980) (a case indicating that the burden of proof can be shifted to the applicant to show that the subject matter of the prior art does not possess the characteristic relied on whether the rejection is based on inherency under 35 U.S.C. § 102 or obviousness under 35 U.S.C. § 103). See MPEP §§ 2112-2112.02. Please also note that the amount of cleavage is not specified in the claims, nor are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, pH, etc. In addition, cleaving the conjugate at this ester bond would release the hydrophobic component (i.e., the acrylic "vinyl type" polymer) from the hydrophilic component (i.e., the PEG). Davaran et al. do not explicitly state that the hydrophobic component will disrupt a membrane when released from the hydrophilic conjugate but the Examiner contends that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and, in addition, Ito et al. state that PMMA, like the one disclosed by Davaran, disrupts PC membranes (e.g., see claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted acrylate groups are preferred."; see also Ito et al., figure 4 showing pH reversible

disruption; see also figure 5; see also figure 6 showing increase in disruption with increase in salt concentration; see also figure 7 comparing PMAA to PEAA). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See also MPEP § 2112-2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus, the claims read on minimal disruption under extreme conditions of temperature, pressure, etc.

For ***claim 38***, Davaran et al. teach a water-soluble conjugate comprising **(a)** a hydrophobic synthetic vinyl-type polymer (e.g., see Davaran et al., page 189, showing methacrylate polymer; see also page 190, column 2, paragraph 2 disclosing use of water-soluble PEGM). Davaran et al. do not explicitly state that the polymer is an endosomal membrane disruptive when released from the hydrophilic conjugate but the Examiner contends that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and Ito et al. disclose a similar pH dependent disruption to that of Applicants' preferred PEAA (e.g., see claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted

acrylate groups are preferred."; see also Ito et al., figures 3-7, especially figure 7). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See also MPEP § 2112-2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus, the claims read on minimal disruption under extreme conditions of temperature, pressure, etc. Davaran et al. also disclose **(b)** a plurality of pendant hydrophilic polyalkylene oxide components (e.g., see scheme 2 and page 190, column 2, paragraph 2 wherein a plurality of PEGs are incorporated into the conjugate via the PEGMs). Finally, Davaran et al. disclose **(c)** a plurality of pH-sensitive linkages (e.g., see scheme and page 190, column 2, paragraph 2 wherein the plurality of PEGs are attached via an ester linkage). Again, Davaran et al. do not explicitly state that each of the pendant polyalkylene oxide components are covalently linked to the polymer through a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5. However, the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al.(e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to

a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5). When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980) (a case indicating that the burden of proof can be shifted to the applicant to show that the subject matter of the prior art does not possess the characteristic relied on whether the rejection is based on inherency under 35 U.S.C. § 102 or obviousness under 35 U.S.C. § 103). See MPEP §§ 2112-2112.02. Please also note that the amount of cleavage is not specified in the claims, nor are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, etc. for extended periods of time..

For ***claim 41***, Davaran et al. teach in addition to the limitations set forth in claim 38 use of a therapeutic or diagnostic agent such as ibuprofen (e.g., see Davaran et al., abstract).

For ***claim 43***, Davaran et al. teach the composition of claim 41, wherein the pH-sensitive linkage is selected from the group consisting of … an ester (e.g., see Davaran et al., page 190, column 2, paragraph 2 wherein PEG is connected to the methacrylate via an ester linkage).

For ***claim 44***, Davaran et al. teach the composition of claim 41, wherein the therapeutic or diagnostic agent is selected from the group consisting of a protein … an organic molecule (e.g., see abstract wherein ibuprofen is disclosed).

For ***claim 45***, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises a random, block, or graft copolymer, wherein the copolymer comprises an alkyl substituted or unsubstituted acrylate group (e.g., see scheme 2 wherein methacrylate is disclosed).

For ***claim 46***, Davaran et al. teach the composition of claim 36, wherein the hydrophobic component comprises poly(ethylacrylic acid), poly(propylacrylic acid), poly(butylacrylic acid), or acrylic acid polymer and copolymers (e.g., see scheme 2 wherein methacrylate is disclosed).

For ***claim 47***, Davaran et al. teach a composition for enhancing transport through a membrane, comprising a hydrophilic conjugate having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage (e.g., see scheme 2 and page 190, column 2, paragraph 1 wherein a hydrophobic methacrylate polymer is linked via a pH-sensitive linkage to a hydrophilic PEG). Davaran et al. do not explicitly state that the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component, but the Examiner contends that this is an

inherent feature of the ester bond as exemplified by Applicants' specification and Theodore et al. (e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"; see also Theodore et al., column 22, last paragraph, "Ester and thioesters are hydrolytically cleaved under acidic or basic conditions [i.e., not neutral]" and thus would be cleaved at pH values less than 6.5). When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980) (a case indicating that the burden of proof can be shifted to the applicant to show that the subject matter of the prior art does not possess the characteristic relied on whether the rejection is based on inherency under 35 U.S.C. § 102 or obviousness under 35 U.S.C. § 103). See MPEP §§ 2112-2112.02. Please also note that the amount of cleavage is not specified in the claims, nor are the conditions under which such cleavage occurs. Thus, the claims read on minimal cleavage under extreme conditions of temperature, pressure, etc. for extended periods of

time. In addition, Davaran et al. disclose a hydrophilic component comprises a polyalkylene oxide (e.g., PEG, see above) and a hydrophobic component comprises a random, block, or graft copolymer, wherein the copolymer comprises an alkyl substituted or unsubstituted acrylate group (e.g., see scheme 2, wherein methacrylate polymer is disclosed). Finally, Davaran et al. do not explicitly state that the hydrophobic component is membrane disruptive and allows enhanced transport through a membrane when released from the hydrophilic conjugate but the Examiner contends again that this is intended use language and thus should not be afforded any patentable weight or, alternatively, is inherently disclosed by the reference since the hydrophobic polymer possesses the same vinyl methacrylate structure as that currently claimed by Applicants and Ito et al. expressly state that PMAA, like the one disclosed by Davaran et al., can disrupt membranes (e.g., see claims 39, 46, and 47; see especially page 11, lines 24 and 25, "Random, block and graft copolymers that include acrylate groups and alkyl substituted acrylate groups are preferred."; see also Ito et al., figures 3-7; especially figure 7). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See also MPEP § 2112-2112.02. Please also note that the amount of disruption is not specified in the claims, nor are the conditions under which such disruption occurs. Thus,

the claims read on minimal disruption under extreme conditions of temperature, pressure, etc.

Response

4. To the extent that Applicants' arguments can be applied against the new rejection set forth above, the following is noted:

[1] Applicants argue that not all the limitations are taught and underline several portions of the claimed composition that are presumably not taught (e.g., see 10/31/07 Response, page 8, paragraphs 1-3).

[1] It is respectfully submitted that all limitations are taught as set forth in the above rejection.

[2] Applicants argue, "The claimed composition differs from the copolymers of the reference in that they are stable at the pH that the reference's copolymers are hydrolyzed [i.e., pH 8.5]" (e.g., see 10/31/07 Response, page 9, paragraph 1).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., composition stable at pH) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claim 36, for example, requires that the linkage between the hydrophilic and hydrophobic components of the water-soluble conjugate

be stable at a pH between 6.8 and 8, not the "entire" composition as purported. As noted in the rejection above, Davaran et al. teach a water-soluble hydrophilic conjugate having a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage (e.g., see Davaran et al., page 189, scheme 2 showing conjugate with methacrylate hydrophobic component; see also page 190, column 2, paragraph 2 wherein the water-soluble PEG is linked via a pH sensitive ester bond to the methacrylate). Although Davaran et al. do no explicitly state that the ester bond in the PEGM is a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 but the Examiner contends that this is an inherent feature of the ester bond as exemplified by Applicants' specification (e.g., see specification, pages 22 and 23, especially page 23, first full paragraph disclosing ester as a "preferred" linkage with these properties; see also page 25, lines 9 and 10, "an ester or acetal bond, which is disrupted upon exposure to a stimulus, for example, a change in pH"). When the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980) (a case indicating that the burden of proof can be shifted to the applicant to show that the subject matter of the prior art does not possess the characteristic relied on whether the rejection is based on inherency under 35 U.S.C. § 102 or

obviousness under 35 U.S.C. § 103). See MPEP §§ 2112- 2112.02. Furthermore, Applicants failed to claim a "length of time" or a "temperature" range for measuring this stability. Thus, Applicants claims read on very short periods of time and very low temperatures that would encompass other more "fragile" linkages that might otherwise be excluded if the temperature, time, pressure, and other relevant environmental conditions were specified (i.e., compare to claim 15 where the length of time, but not the temperature, pressure, etc., is at least specified).

[3] Applicants argue, "the reference's copolymers are not hydrolysable at a pH less than 6.5 to release ibuprofen" (e.g., see 10/31/07 Response, page 9, paragraph 1).

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., hydrolysable at a pH less than 6.5 to release ibuprofen) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For example, claim 36 does not require the release of a drug like ibuprofen. Likewise, claim 38 only requires polyalkylene oxide components, not the drug, to be linked via a pH sensitive linkage. Claim 41 also states that the pH-sensitive linkages bind pendant polyalkylene oxide components, not the drug. Likewise, claim 34 reads that the composition of claim 36 further comprises a therapeutic agent but does not specify that it has to be cleaved under the conditions specified by Applicants to release said therapeutic.

[4] Applicants argue, "Hydrolysis of the thioester bond releasing ibuprofen does not provide a hydrophobic polymer that is membrane disruptive ... hydrolysis of the ester linkage

intermediate the PEG group and the poly(methylacrylate) backbone does not provide a hydrophobic component (i.e., vinyl polymer) that is membrane disruptive [either] ... [because] a poly(methylacrylic acid) ... is not membrane disruptive [as evidenced by Exhibit A] ... While poly(ethylacrylic acid) and poly(propylacrylic acid) are effective in membrane disruption, poly(methacrylic acid) is not ... [and] there [is] no apparent reason to further modif[y] Davaran's teaching to arrive at the claimed invention" (e.g., see 10/31/07 Response, pages 10 and 11).

[4] The Examiner respectfully disagrees. The Stayton declaration under 37 CFR 1.132 filed 10/31/07 [i.e., exhibit A] is insufficient to overcome the rejection of claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 based upon 35 U.S.C. §§ 102/103 as set forth in the last Office action because: (1) The declaration shows at least "minimal" membrane disruption results from the use of PMAA (e.g., see Exhibit A, figure 2, pH 5 and 5.4 wherein the disruption was greater than zero; see also figure 3 comparing PMAA to control). Thus, PMAA meets the claimed requirement for membrane disruption because no "basement" value is set. (2) It refers only to hemoglobin hemolysis and, as such, does not provide evidence that PMAA would not disrupt other membranes (i.e., is not commensurate in scope with the claims). See MPEP § 716. For example, Ito et al. expressly state that PMAA disrupts PC membranes (e.g., see Ito et al., figure 6). (3) Applicants have failed to test conditions that are known to be outcome determinative. For example, Ito et al. state that increasing salt concentration will increase the amount of disruption in a membrane (e.g., see Ito et al., figure 6). However, Dr. Stayton never states that any other salt concentrations were tested. Likewise, Dr. Stayton never presents any evidence for pH values below 5 (e.g., see figure 2) even though PMAA is "activated" at lower pH values (e.g., see Ito et al., figure 7, showing significant activation at pH 4). This "omission" in pH

values is highly relevant considering the known activation curves for these "smart" pH-dependent polymers.

Claim Rejections - 35 USC § 103

5. Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davaran et al. (Davaran et al., "Hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydroyzable thioester bond" *Eur. Polym. J.* **1998**, *34(2)*, 187-192) in view of Arnold (U.S. Patent No. 4,571,400) (Date of Patent is **Feb. 18, 1986**) and Vinogradov et al. (Vinogradov et al., "Self-Assembly of Polyamine-Poly(ethylene glycol) Copolymers with Phosphorthioate Oligonucleotides" Bioconjugate Chem. **1998**, *9*, 805-812) (of record) as evidenced by Applicants' specification and Baroni et al. (Baroni et al., "Effect of ibuprofen and warfarin on the allosteric properties of haem-human serum albumin" *Eur. J. Biochem.* **2001**, 268, 6214-6220) and Ito et al. (Ito et al., "Control of Water Permeation by pH and Ionic Strength through a Porous Membrane Having Poly(carboxylic acid) Surface-Grafted" Macromolecules **1992**, 25, 7313-7316) and Theodore et al. (U.S. Patent No. 6,358,490) (Date of Patent is **March 19, 2002**).

For ***claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47***, Davaran et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

The prior art teaching of Davaran et al. differ from the claimed invention as follows:

For ***claims 16 and 17***, Davaran et al. fail to teach the composition of claim 36 further comprising a pharmaceutically acceptable carrier for delivery of the conjugate to a cell or organelle.

For ***claim 19***, Davaran et al. fail to teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is an antisense nucleotide, ribozyme, ribozyme guide sequence, triplex forming oligonucleotide, or gene.

However, Arnold teaches the following limitations that are deficient in Davaran et al.:

For ***claims 16 and 17***, Arnold (see entire document) teaches the use of a wide range of pharmaceutically acceptable carriers for use with ibuprofen (e.g., see Arnold, column 3, lines 1-55), which would encompass the ibuprofen disclosed by Davaran.

For ***claim 19***, Vinogradov et al. teach the composition of claim 34, wherein the therapeutic, diagnostic, or prophylactic agent is, for example, an antisense nucleotide (e.g., see page 807, right col., line 8 thru page 808, right col., line 23; see also page 806, left col., lines 44-65).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to use a pharmaceutically acceptable carrier with the ibuprofen complex disclosed by Davaran et al. because Arnold explicitly state that pharmaceutical carriers can be used in conjunction with ibuprofen (e.g., see Arnold, column 3, lines 1-55; see also claims 4 and 6). A person of ordinary skill in the art would have been motivated

to use a pharmaceutically acceptable carrier because Arnold teach that these carriers are useful for administering the drug to a mammal and claim it as a "preferred" embodiment (e.g., see Arnold, column 3, lines 1-55; see also claims 4 and 6). Finally, a person of ordinary skill in the art would reasonably have expected be successful because the use of pharmaceutically acceptable carriers is well known and Arnold explicitly state that it can be used in conjunction with ibuprofen, which would encompass the ibuprofen disclosed by Davaran.

In addition, it would have *been prima* facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the antisense oligonucleotides as disclosed by Vinogradov et al. for the ibuprofen as disclosed by Davaran et al. because Davaran et al. teach that any therapeutic molecule can be attached to their hydrophilic copolymers (e.g., see Davaran et al., Introduction), which would encompass the antisense oligonucleotides disclosed by Viogradov et al. Furthermore, a person of ordinary skill in the art would have been motivated to use the hydrophilic copolymers to prevent degradation of the oligonucleotides and/or side effects (e.g., see Davaran et al., Introduction). Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Vinogradov et al. teach that the anti-sense oligonucleotides can be conjugated to PEG polymers like the PEG polymer disclosed by Davaran.

Response

6. To the extent that Applicants' arguments can be applied against the new rejection set forth above, the following is noted:

Applicants argue that the deficiencies noted above are not cured by the teachings of Vinogradov and Arnold (e.g., see 10/31/07 Response, page 12).

As noted above, there are no deficiencies in Davaran and Baroni. Thus, Applicants' arguments are moot.

Allowable Subject Matter

7. Claims 39 and 42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639